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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,083	07/13/2001	Timothy I. O'Brien	D6223CIP/C/D	4623

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,083	O'BRIEN, TIMOTHY I.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 22-31 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 26-31 is/are allowed.

6)☒ Claim(s) 22-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/22/2003 has been entered.

2. Claims 1-21 and 32-39 have been canceled in the amendment filed as Paper No. 15 on 11/14/2003.

3. Claims 22-31 are under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

5. The rejection of claims 22-25 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained and made again.

Applicant claims and discloses a method for vaccinating an individual against SCCE or fragments thereof and the individuals either have cancer or are suspected of getting cancer. Applicants disclose a method of vaccinating an

individual against stratum corneum chymotrytic enzyme (SCCE) comprising the steps of inoculating an individual with the stratum corneum chymotrytic enzyme or fragment thereof, wherein the SCCE or fragment thereof lacks SCCE protease activity (see pages 22-23 of the specification). Applicants have provided insufficient direction or guidance to assist one skilled in the art in the selection of all possible SCCE vaccine fragments, nor is there evidence provided that all such fragments would be therapeutically effective. Further, the as-filed specification fails to address the following issues as related to the claimed SCCE cancer vaccines:

1) what amount of the stratum corneum chymotrytic enzyme or fragments thereof are considered to be therapeutically effective for a desired "protective effect" in a mammal;
2) what defines a "protective effect" against a tumorous disease in a mammal;
3) what would one skilled in the art compare the claimed method of vaccination to in order to ascertain that the "protective effect" against a tumorous disease was achieved.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual tumorous disease. It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Forni et al (Cancer Research, 2000, 60; 2571-2575) disclose tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack (see page 2571, right column). Mouse models show that elicitation of a significant immune response in patients with advanced tumors is exceedingly difficult, and only a minority of tumor-

bearing mice are cured. "As a tumor increases in size, it becomes refractory to immunotherapy" (see page 2571, left column). A similar picture is emerging from Phase I immunotherapy trails where only a few patients with established tumors display objective and in any event temporary responses (see page 2571, right column). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy *in vivo*. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

Donnelly J. (Nature Medicine, 11(9): 1354-1356, Nov. 2003) states "treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future" (see page 1354 lines 13-17). Further, DeGruijl T. D. et al (Nature Medicine, 5(10): 1124-1125, Oct. 1999) state that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. DeGruijl also states "precise correlates of clinical effects and immunological responses have been lacking" (see page 1124, left column).

It has been art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to bedside) is a quantum leap. Bodey B. et al acknowledge that general immune activation directed against the target antigens contained within cancer vaccines has been documented in most cases and tumor specific cytotoxic T lymphocytes (CTLs)

can be isolated from the solid tumors, draining lymph nodes, metastatic effusions, and peripheral blood of cancer patients. However, attempts at active specific immunotherapy using cancer vaccines have met with little success in clinical trials (see abstract and page 2668). "Peptide vaccination against tumor antigens can induce powerful systemic CTL responses. However, in the majority of patients, no tumor regression is noted" (see page 2673, left column). Lee et al (Journal of Immunology 163: 6292-6300, 1999) also disclose that a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the peripheral mononuclear cells of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules (see page 2673, right column). "Use of cancer vaccines to stimulate the immune system may be in vain, if the particular tumor associated antigens represented in the vaccine preparation are no longer present on the most advanced subsets of cancer cells" (see pages 2673-2674).

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to induce tumor immunity to prevent tumor recurrence and to eliminate residual tumorous disease by inoculating an individual with the SCCE or fragments thereof, wherein the SCCE or fragments thereof lack protease

activity. The specification does not teach how to extrapolate data obtained from SCCE-peptide specific cytotoxicity assays (see the declaration of Dr. Timothy J. O'Brien filed as Paper No. 9 on 2/19/2003) to the development of effective cancer vaccines that prevent tumor occurrence or even result in tumor regression. The specification does not address how inoculating an individual with compositions comprising the SCCE or fragments thereof overcome the back-and-forth struggle between host and tumor, a process which creates highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells.

In view of the lack of the predictability of the art to which the invention pertains, the lack of established clinical protocols for effective cancer therapies, undue experimentation would indeed be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for vaccinating individuals against cancer, commensurate in scope with the claimed invention.

6. The amendment filed 11/14/2003 has been carefully considered, but is deemed not to be persuasive. The response states that the SCCE peptides having binding motifs for HLA class I molecules are able to induce specific cytotoxic T lymphocyte responses as evidenced by the declaration of Dr. Timothy J. O'Brien filed as Paper No. 9 on 2/19/2003. Applicant's continue "The purpose of vaccination is to provide an antigen against which the body will launch an

immune response; subsequently, should the body be exposed to the antigen a second time, the immune system will "remember" the antigen and quickly eliminate the cells presenting the antigen, in order to prevent disease" (see pages 6-7 in the Response After Final filed as Paper No. 15 on 11/14/2003). It is acknowledged that SCCE peptides 32 and 33 are capable of eliciting an immune response as evidenced by the declaration of Dr. Timothy J. O'Brien. The issue in the instant application is not whether the SCCE peptides can induce an immune response, but rather can the SCCE peptides prevent cancer? As evidenced by the references cited in the Response to Arguments there is no correlation between immune response and clinical efficacy with respect to cancer vaccines. Further, applicants have provided no evidence that the claimed method of vaccination results in cancer prevention or even tumor regression either in animal models, clinical studies or otherwise.

Conclusions

7. Claims 26-31 are in condition for allowance.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (703) 605-1200. The examiner can normally be reached at (703) 605-1200 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, can be reached at (703) 308-3995. Any inquiry of a general nature or relating to the status of this

application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
703-605-1200

LARRY R. HELMS, PH.D
PRIMARY EXAMINER